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JEAN M. DUVALL
ATHENA NEUROSCIENCES
800 GATEWAY BLVD.
SAN FRANCISCO, CA 94080

DATE MAILED: 06/25/96

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 6-10-96 (3-28-96 P) ☐ This action is made final.

A shortened statutory period for response to this action is set to expire three month(s), Ø days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☒ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474..
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 42-47 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☒ Claims 1-41 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 42-47 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

Part III DETAILED ACTION

1. The amendments and response to the restriction requirement in Paper No. 9, filed 3-28-96 and Paper No. 12, filed 6-10-96 have been entered into the record. Claims 1-41 have been cancelled. Claims 42-47 are pending and under examination.

Drawings

2. This application has been filed with informal drawings which are acceptable for examination purposes only. The drawings are objected to by the draftsperson under 37 C.F.R. 1.84 or 1.152. See PTO-948 for details. Applicant is required to submit a proposed drawing correction in response to this Office action. However, correction of the noted defect can be deferred until the application is allowed by the examiner.

Specification

3. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an enabling disclosure for an in vivo method for screening a compound to determine its ability to alter the amount of an Aβ (x -≥ 41) peptide in the cerebrospinal fluid (CSF) in a non-human animal used as a model of Alzheimer's Disease.

The claims are drawn to methods for screening for compounds to alter the amount of Aβ (x -≥ 41) peptide in the cerebrospinal fluid (CSF) in a non-human animal used as a model of Alzheimer's Disease. The specification fails to teach appropriate routes of administration such that the compound effectively reaches the brain, the duration of *in vivo* treatment and appropriate time frames for the first and second collection of samples for analysis. It is unclear if the animal models display the quality and /or quantity of deposits change in an age-dependent manner. The lifespan of the aged non-human primate and the transgenic rodents are significantly different. If the levels change over time, as they do in human disease, then absent teaching of suitable time frames for testing it would be unpredictable if any observed change predictably correlates with an effect of the compound. In view of the lack of teachings in the specification, the unpredictability of an correlation and lack of a working example it appears that undue experimentation would be required in the absence of further guidance from applicants.

Several points are of significant note with respect to animal models and Alzheimer's Disease. The art recognizes no animal model which predictably and reproducibly displays all the histopathological (β-amyloid deposits and neurofibrillary tangles) and neuropsychological aspects of Alzheimer's Disease. Therefore, there exists no art accepted animal model of human Alzheimer's Disease. The only animals which to a limited extent mimic the amyloid depositing component of Alzheimer's Disease are the aged non-human primate and the transgenic animal. Both of these models differ in significant fashion from the human disease. Both aged non-human primates and transgenic mice lack neurofibrillary tangles which are always present in human disease.

While the aged human primate displays similar β-amyloid plaques as assessed by histochemical staining is similar to that found in humans, the specification fails to teach that the same Aβ (x -> 41) peptides are present at similar levels in the cerebrospinal fluid of this animal as compared to the human, such that one of skill in the art could reproducibly assess effect of the compound administered *in vivo* by applying the teachings for the human. It is therefore unknown if the metabolic events which give rise in the aged-non human primate predictably and reproducibly correlate with those events observed humans. Because the aged non-human primate model does not display all the hallmarks of the human disease and the specification fails to teach that the Aβ (x -> 41) peptides are present in the same compartments with similar sequences, it is unpredictable that the amyloid is metabolized in the same fashion to the same peptide fragments. Thus, it is not apparent form the teachings of the specification that the teachings for CSF for humans can be predictably and reproducibly applied to the aged non-human primate. In addition, as with humans not all aged non-human primates develop cerebral β-amyloidosis. Uno et al teach that in the autopsy of 186 rhesus monkeys aged 20-36 years, that the incidence of plaque formation with cerebral angiopathy was observed in 51 aged brains (60%) was observed by histopathological examination (Uno et al, Annals of the New York Academy of Sciences, 1993, pages 232-235). Uno et al teach that:

> "As in aged human brains, the incidence of age-dependent cerebral β-amyloidosis in captive rhesus monkeys showed great individual variation." (page 232, see abstract)

The specification fails to teach how to predictably and reproducibly identify those living aged-animals which display the requisite β-amyloidosis pathology in order to test a compound of

interest. Given the notable differences of the aged non-human primates as compared to humans in combination with the lack teachings of the specification with respect to correlation of the aged non-human primate and human disease and lack of working examples, it would appear that undue experimentation would be required to practice the *in vivo* screening methods in aged non-human primates. In addition, the specification fails to teach that any difference in Aβ (x-≥ 41), either an increase or decrease, when compared with a predetermined amount, predictably and reproducibly correlates with a change in the mental or physical status of an animal model such as the aged non-human primate, either beneficial or detrimental after treatment using the instantly claimed assay. Since the specification fails to teach that the levels of Aβ (x-≥ 41) present in a sample predictably and reproducibly correlates with an improvement, worsening or exacerbation of the disease state with Aβ (x-≥ 41) presence in the CSF or any other biological fluid or tissue. Absent a predictable and reproducible correlation of Aβ (x-≥ 41) with an altered mental or physical status of the animal models and in the absence of a working example, it is unknown if the instant assay is capable of detecting alterations in the amount of Aβ (x-≥ 41) peptides by the test compound and it therefore would appear to require undue experimentation on the part of the skilled artisan to screen for compounds which alter the amount of Aβ (x-≥ 41) present in the CSF or biological fluid in an animal model for Alzheimer's Disease.

As to the transgenic rodent models, at the time that the invention was made, no reported transgenic rat models existed and all of the reported transgenic mice bearing DNA constructs for the APP precursor or parts thereof have not developed convincing pathological changes similar to what is observed in patients with Alzheimer's disease (Fukuchi et al,

Annals of the New York Academy of Sciences, 1993, pages 217-223). Those transgenic mice that have been produced using the βAPP-751 or βAPP-695 demonstrate conflicting pathologies. The βAPP-695 transgenic mouse under the control of the neural-specific enolase promoter did not develop β-amyloid deposits. Although, the βAPP-751 transgenic mouse under the control of the neural-specific enolase promoter did demonstrate some β-amyloid deposits these animals do not produce plaques with the same staining characteristics as those found in humans (Fukuchi et al, Annals of the New York Academy of Sciences, 1993, page 220) and moreover do not display the neurofibrillary component of the disease. Fukuchi et al (page 220, second full paragraph) teach that:

> "These results suggests that changes in ratios of neuronal βPP isoforms (especially increase of βPP-751) may lead to amyloidogenesis. Much more complete analysis of these transgenic mice, however, is necessary for acceptance as models for AD."

The notable differences in the staining characteristics, suggests that the amyloid deposited in the βAPP-751 transgenic mouse may not be the same as that deposited in human disease. In addition, the specification fails to teach how to and how much CSF must be collected from the transgenic rodent model in order to reproducibly detect Aβ (x -≥ 41) peptide. The specification teaches that 100 ul of human CSF is required by the typical ELISA (see specification pages 29-30). With regard to the collection of rodent CSF, the specification fails to teach how to reproducibly collect CSF from a transgenic mouse or other rodent. Even if CSF could be collected from a mouse or other rodent, it is not apparent that 100 ul of CSF could in fact be removed from a transgenic mouse, even once, without resulting in the death of the animal. Absent, a direct demonstration of the actual mass level of Aβ (x -≥ 41) peptides (i.e. ng/ml) in the CSF of a transgenic mouse, it is not apparent that the disclosed

assay for humans has the requisite sensitivity to detect Aβ (x -≥ 41) peptides in decreased volumes which would be reasonably required in order to ensure the survival of the screening animal in order to collect the second amount at some later time point after administration of the compound of interest, as is required by the instant claims. Because the transgenic rodent models described by the art are restricted to murine models and the murine models do not display all the hallmarks to the human disease and the specification fails to teach that the actual sequences of the Aβ (x -≥ 41) peptide are present and functionally identical in the CSF of transgenic rodents and humans, it is unpredictable that the transgene amyloid is metabolized and compartmentalized in the same fashion. The specification fails to teach that any non-human animal model produces the same Aβ (x -≥ 41) peptides in the cerebrospinal fluid (CSF) as found in humans with this disease such that one of skill in the art could predictably interpret the outcome of the *in vivo* screening method. Thus, it is not apparent form the teachings of the specification that the teachings for humans can be predictably and reproducibly applied to a transgenic rodent. Given the lack of correlation of the transgenic rodent models reported with human disease and in view of the lack teachings of the specification with respect to correlation of the metabolism of β-amyloid in the transgenic rodents with human disease and lack of working examples, it would appear that undue experimentation would be required to practice the *in vivo* screening methods in a transgenic rodent.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an enabling disclosure for an *in vivo* method for screening a compound to determine its ability to alter the amount of an Aβ (x -≥ 41) peptide in the cerebrospinal fluid (CSF) in a

non-human animal used as a model of Alzheimer's Disease. First, the specification fails to teach the presence of Aβ (x -≥ 41) peptide in the CSF of in models of amyloidosis, such as the non-human primate or transgenic mouse predictably and reproducibly correlates with the histopathological findings in these animal models. The specification fails to teach that any alteration in the Aβ (x -≥ 41) peptide in the CSF predictably and reproducibly correlates with the histopathological changes in these animal models. Moreover, the specification fails to teach whether the quality and/or quantity of the deposits change in an age-dependent manner in the animal model under the time frame of the in vivo study. The formation of cerebral β-amyloid plaques is a ongoing process in humans and plaque density increases in severity until death. The specification fails to teach appropriate time frames in the individual amyloid models to assess the basal levels, the amount of time administer the test compound and assess treated levels to predictably and reproducibly assess the effect of the compound. Because the basal levels may change with increasing time, one of skill in the art could not predictably and reproducibly assess the effect of the reagent across an unknown or undefined time frame in which the levels of the Aβ (x -≥ 41) peptide may be reasonably be expected to change. Since applicants fail to teach appropriate time frames for the steps of the *in vivo* screening methods for the corresponding animal models, it would appear that undue experimentation would be required on the part of the skilled artisan to practice the invention as claimed. The specification fails to teach that any difference in Aβ (x-≥ 41), either an increase or decrease, when compared with a predetermined amount, predictably and reproducibly correlates with a change in the histopathological findings in the models of amyloidosis, either beneficial or detrimental. Since it is unclear that the presence of the

histopathology in the animal models predictably and reproducibly correlates with the presence of Aβ (x -≥ 41) peptide in the CSF or any other biological fluid (i.e. serum), one of skill in the art would not be able to assess the ability of a test compound to alter the level of Aβ (x -≥ 41) peptide in any biological fluid including CSF. Even if, the transgenic animal or the aged-non human primate demonstrated similar findings to the human, the specification fails to teach the routes of administration of the compound to allow the compound to traverse the blood brain barrier, the time period for administration of the compound (i.e. days to years) for which one of skill in the art would be able to predictably and reproducibly interpret the alleged affect of the compound using the instantly claimed screening method. Absent further guidance from applicants, and in the absence of a predictable correlation of the histopathology in the animal models with the presence of Aβ (x -≥ 41) peptide in any biological fluid including CSF, it would require undue experimentation on the part of the skilled artisan to screen for agents with alter the amount of Aβ (x -≥ 41) peptide.

5. Claims 45-47 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

6. The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an enabling disclosure and/or lack of an adequate written description on how to make and use a transgenic animal including mice having an expression cassette that drives expression of a sequence which encodes the Swedish mutation of an APP gene for use in an *in vivo* screening method for agents which alter the amount of Aβ (x -≥ 41) peptide in the cerebrospinal fluid (CSF). The specification also fails to teach if the human homologue can be distinguished from the non-human animal used to make the transgenic animal such that

the effect on only the human homologue can be assessed. In general, the production of transgenic animals is not routine in the art and requires a high level of skill, with the ultimate stable expression of the APP gene of interest in germline of the transgenic animal in the appropriate tissue of interest which also displays β-amyloid deposits and is capable of germline transmission is unpredictable because the integration of the cassette into the genome is random and the stability and degree of expression of the transgene is unpredictable even using strong promoters. This unpredictability in the production of transgenic animals is significantly compounded by the teaching of the art which specifically teach that the generation of transgenic animals displaying the even the β-amyloid deposits in the brain is highly unpredictable and expression is variable (Fukuchi et al, Annals of the New York Academy of Sciences, 1993, pages 217-223) even if the gene is inserted with a expression cassette using the neural-specific enolase promoter. The specification moreover, clearly lacks adequate written guidance as to the description of procedural steps of how to make the expression cassette with the Swedish mutation, what isoform of the APP (965, 751 or 770) is employed, how to make the transgenic animal with this cassette and whether the animal so produced can be predictably reproduced to generate other identical animals and also have the progeny display β-amyloid deposits. Applicants, instead rely on improper incorporation by reference of US application 08/143,697. Applicants can not incorporate essential enabling material by reference from a US application (see M.P.E.P. § 608.01(p)). Given the unpredictability in the generation of APP transgenic animals, and in view of the lack of adequate written description, and lack of working examples it appears that absent further guidance from applicants, it would require undue experimentation on the part of the

skilled artisan to make the Swedish transgenic animal for use in an *in vivo* screening method for agents which alter the amount of Aβ (x -≥ 41) peptide in the cerebrospinal fluid (CSF). Even if the specification were enabling for the production of the Swedish transgenic animal, the specification would not be enabling for reasons set forth in paragraph 4 *supra*.

7. Claims 45-47 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

8. The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an enabling disclosure and/or lack of an adequate written description on how to assay for Aβ (x-≥ 41) when the soluble Aβ (x-≥ 41) detected does not include the junction spanning the region disposed between amino acid residues 13 to 28. As to claims 42-47, the specification fails to teach a predictable and reproducible measurement of the amount of Aβ (x-≥ 41) when the soluble Aβ (x-≥ 41) detected does not include the junction spanning the region disposed between amino acid residues 13 to 28. The specification fails to teach predictable and reproducible binding reagents and methods of detection for one or more soluble Aβ (x-≥ 41) when x≥17. However, the specification does teach predictable and reproducible detection of soluble Aβ peptides containing at least amino acids 13-42 using the monoclonal antibody 266. The specification teaches the use of this antibody as a capture antibody specific for a junction region on AB fragment disposed between amino acid residues 13 to 28 (p 19; i.e. "266") in a patient sample. The specification also teaches that this antibody will not bind the soluble fragment Aβ 17-28. Thus, the specification teaches that the minimal which could be predictably and reproducibly detected **must encompass** the junction

region spanned by amino acid residues 13 to 28 in order to detect Aβ (x-≥ 41) peptides associated with Alzheimer's Disease.

9. Claims 42-47 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

10. No claim is allowed.

11. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

(a) Cordell (U.S. Patent No. 5,387,742) teaches transgenic mice displaying the amyloid-forming pathology of Alzheimer's Disease.

(b) Games et al (Nature, 373(6514):523-527, February 9, 1995) teaches transgenic mice overexpressing V717F β-amyloid precursor protein.

(c) Lannfelt et al (Behavioral Brain Research, 57:207-213, 1993) teaches the Swedish mutation with produces both a Lys-->Asn and a Met-->Leu amino acid change at codons 670 and 671, at the N-terminus of β-amyloid.

(d) Seubert et al (Nature, 359:325-327, September 24, 1992) teaches specific antibodies and assays for the isolation and quantification of soluble Alzheimer's β-peptide from biological fluids.

(e) Iwatsubo et al (Neuron, 13:45-53, July 1994) teaches End-specific Aβ monoclonal antibodies for Aβ42(43).

(f) Vigo-Pelfrey (J. Neurochemistry, 1993, 61:1965-1968) teaches Aβ (x-≥ 41) peptides.

(g) Suzuki et al (Science 264:1336-1340) teaches increased percentage of long amyloid β protein ($A\beta_{1-42}$) secreted by familial amyloid β protein mutants.

12. The claimed invention is only free of the prior art inasmuch as the art fails to suggest detecting a baseline level of the Aβ peptides in CSF, administering a test compound, detecting the level of the antigen subsequent to administration of the test compound and subsequently comparing the baseline value to the post administration value.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy, Ph.D. whose telephone number is (703) 305-7555. The examiner can normally be reached on Monday-Friday from 6:30 AM to 3:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marian Knode, can be reached at (703) 308-4311.

Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application should be directed may be submitted to Group 1800 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The FAX number for Art Unit 1806 is (703) 308-4242.

Marian C. Knode

PAD
Patricia A. Duffy, Ph.D.
June 24, 1996

MARIAN C. KNODE
SUPERVISORY PATENT EXAMINER
GROUP 1800